A new prognostic score supporting treatment allocation for multimodality therapy for malignant pleural mesothelioma- A review of 12 years' experience

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Abstract: INTRODUCTION Treatment of malignant pleural mesothelioma (MPM) remains a clinical challenge. The aim of this study was to identify selection factorsfor allocation of MPM patients to multimodal therapy based on survival data from 12 years of experience. METHODS Eligible patients had MPM of all histological subtypes with clinical stage T1-3 N0-2 M0. Induction chemotherapy consisted of cisplatin/gemcitabine (cis/gem) orcisplatin/pemetrexed (cis/pem), followed by extrapleural pneumonectomy (EPP).Multivariate analysis was performed to assess independent prognosticators for overall survival (OS). A Multimodality Prognostic Scorewasdeveloped based on clinical variablesavailable before surgery. RESULTS From May 1999 to August 2011, 186 MPM patients were intended to be treated with induction chemotherapy followed by EPP. Hematologic toxicity was significantly less frequent after cis/pemcompared to cis/gem, but no difference in response or OS between the regimens.128 patients underwent EPP with a30-day mortalityof4.7%. 52% percent of the patients received adjuvant radiotherapy. The median OSof patients undergoing EPP was significantly longer with 22months (95%CI:20-24) as compared to 11 months (9-12) for patients treated without EPP.Aprognostic score was defined considering tumor volume,histology, CRP,andresponsetochemotherapythat identified patient groupsnot benefittingfrom multimodality treatmentwhich was confirmed in an independent cohort. CONCLUSION Patients receiving induction chemotherapy followed by EPP for MPM of all histological subtypes and irrespective of nodal statusshowed a median survival of 22months. A prognostic score is proposed to help patient allocation for surgery after validation in an independent cohort.

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Abstract

Introduction: Treatment of malignant pleural mesothelioma (MPM) remains a clinical challenge. The aim of this study was to identify selection factorsfor allocation of MPM patients to multimodal therapy based on survival data from 12 years of experience.

Methods: Eligible patients had MPM of all histological subtypes with clinical stage T1-3 N0-2 M0. Induction chemotherapy consisted of cisplatin/gemcitabine (cis/gem) orcisplatin/pemetrexed (cis/pem), followed by extrapleural pneumonectomy (EPP).Multivariate analysis was performed to assess independent prognosticators for overall survival (OS). A Multimodality Prognostic Scorewasdeveloped based on clinical variablesavailable before surgery.

Results: From May 1999 to August 2011, 186 MPM patients were intended to be treated with induction chemotherapy followed by EPP. Hematologic toxicity was significantly less frequent after cis/pemcompared to cis/gem, but no difference in response or OS between the regimens.128 patients underwent EPP with a30-day mortalityof4.7%. 52% percent of the patients received adjuvant radiotherapy. The median OSof patients undergoing EPP was significantly longer with 22months (95%CI:20-24) as compared to 11 months (9-12) for patients treated without EPP.Aprognostic score was defined considering tumor volume,histology, CRP,andresponsetochemotherapythat identified patient groupsnot benefittingfrom multimodality treatmentwhich was confirmed in an independent cohort.

Conclusion: Patients receiving induction chemotherapy followed by EPP for MPM of all histological subtypes and irrespective of nodal statusshowed a median survival of 22months. A prognostic score is proposed to help patient allocation for surgery after validation in an independent cohort.

Keywords: *extrapleural pneumonectomy - inductionchemotherapy – selection score malignant pleural mesothelioma –multimodality therapy*

Treatment of malignant pleural mesothelioma (MPM) patients continues to be a clinical challenge. Advances overthe last decades, including better understandingof tumor biology and improved quality of complete macroscopic resection, have changed the scepticalattitude towards this disease. This is a result of rising experiences with multimodality (MM) treatment strategies associated with a median survival up to 59 months in selected patients[1-4]. One of the most challenging questions is the selection of patients for aggressive treatment, considering the limited prognosis of MPM patients in general.To identify patient subgroupsnot benefitting from MM therapy and therefore to exclude those from surgery would be desirable.

In the presentreport we analysedone of the largest series ofconsecutively treated patients with induction chemotherapy (cis/gemor cis/pem) followed by extrapleural pneumonectomy (EPP). We decided to establisha new Multimodality Prognostic Scoreusing clinical variables for the decision to perform surgery.

Materials and Methods

Patients and Indications

MPM patients treated at the Division of Thoracic Surgery of the University Hospital Zurichbetween May 1999 andAugust 2011were analysed. Eligibility criteria were biopsyproven MPM of any histological subtype, clinical stage T1-3, N0-2, M0 disease[5], and resectabilitybased on the decision of aninterdisciplinary tumorboard including a thoracic surgeon. Other inclusion criteria were as described previously[2]. For staging procedures patients underwent CT scan of the chest and / or PET-CT scan before and after chemotherapy.In 81% videomediastinoscopywas performed for mediastinal staging to rule out N3 disease. Patients treated as part of theSAKK multicentre study(SAKK 17/04; ClinicalTrials.gov Identifier: NCT00334594) (n=45) are also included in the analysis. The treatment protocol was performed in compliance with the principles of good clinical practice, the Helsinki declaration, and institutional guidelines.

Treatment Plan

Induction chemotherapyconsisted of three cycles of cisplatin and gemcitabine (cis/gem) or since March 2003 of cisplatin and pemetrexed(cis/pem) as described previously [6].

Surgery(EPP) was performed within 6 weeks after completion of the last cycle of chemotherapy as described previously[6].Final pathological staging was carried out following the TNM staging system[7].

Radiotherapy was performed according to definite tumor stage and if high-risk zonesweredefined by the operating surgeon or according to SAKK 17/04treatment protocol. Different radiation techniques and doses were applied over the years (3D-conformal radiotherapy and IMRT).Overall 67 patients (52%) received adjuvant radiotherapy (12 patients in IMRT technique) after induction chemotherapy and EPP.

Analysis of data

Data were collected from medical records archived in our data management program KISIM Version 4.816 (retrospective analysis 1999-2004, prospective documentation since 2004).

All consecutive patients intended to be treated with inductionchemotherapy and EPP were retrospectively analysed for toxicity of chemotherapy and survival. Toxicities assessed were grade °III/°IVhaematological toxicity, grade °III/°IVnephrotoxicity, and unscheduled hospitalizations due to chemotherapy.

Response to chemotherapy was evaluated by modified RECIST criteria by one independent observer (T.F)[8] in 128 cases with available pre and post chemotherapy imaging as was the tumor volume (T.F., D.N.-K.) which was assessed by the help of a semi-automated dedicated software (Myrian®; Intrasense, Paris, France) asdescribed previously [9].

Patients undergoing EPP after induction chemotherapy were evaluated for putative prognostic factors for overall survival (OS)according to Simms et al.[10]. Continuous variables were dichotomized by data driven approaches. The putative factors described for an association with outcomewere: sex, age (≤61 years vs. >61 years), exposure to asbestos, smoking, weight

loss (≥10% body weight), chest pain, ECOG-Performance status (0 vs. 1 vs. 2), white blood cell count (≤9.6 G/l vs. >9.6 G/l), platelets count (≤400 G/l vs. >400 G/l), haemoglobin amount (≤ 117 g/l vs.>117 g/l), CRP level (≤30 mg/l vs. >30 mg/l), LDH (≤480 U/l vs. >480 U/l), cN2 assessed by mediastinoscopy, pre-chemotherapy histology and definitive histology (epithelioid vs. non-epithelioid), extend of resection (R0/1 vs.R2), RECIST factor (partial remission (PR)orstable disease (SD) vs. progressive disease (PD)),tumor volume pre and post chemotherapy (≤500 ml vs. >500 ml), ypT-stage, nodal status (ypN0 vs. ypN1/2), lymph node ratio (positive lymph nodes: regional and mediastinal/ all resected lymph nodes), trocar infiltration, IMIG-stages, regimen of chemotherapy (cis/gem vs. cis/pem), radiotherapy (adjuvant radiotherapy vs. no adjuvant radiotherapy), EORTC-Score (European Organization for Research and Treatment of Cancer-classification)[11].

Statistical analysis was carried out using the software package SPSS for Windows, 20.0.0 (SPSS Inc., Chicago, IL, USA). Categorical data are given as total number and percentages and were compared between groups using Fisher's exact test. Continuous data are given as median with range.

Median survival time was assessed by Kaplan-Meier curves and the influence of the different prognostic factors was analysed by log rank-test. Survival time was calculated as time between application of the first cycle of chemotherapy and time point of death or last follow-up. For comparison of continuous variables in two independent groups we used the Mann-Whitney U test.

Two-sided p-values lower than 0.05 were considered statistically significant. In order to study the joint influence of the different factors on survival in a multivariate analysis, a stepwise Cox regression was performed including all prognostic factors being significant in the univariate analysis excepting factors being represented already in the score.

Based on our clinical experience, results from the literature[12, 13],and prognosis relevant factors derived from our survival analyses, we established a new Multimodality Prognostic

Score(MMPS) to identifysubgroups of patients not benefitting from MM therapy. The score contains 4 items with a maximum possible score of 4 if the patient presented all four conditions and 0 if none were present: Tumor volume before chemotherapy >500 ml, non-epithelioid histological subtypein the diagnostic biopsy before chemotherapy, CRP value >30 mg/lbefore chemotherapy,and progressive diseaseafter chemotherapy. A second score using the same variables without progressive disease after chemotherapy was tested in order to evaluate factors being available at initial patient evaluation.

The predictive power of our new MMPS was compared to the existing EORTC score at one and two years using time-dependent ROC curve estimation using the R package timeROC(version0.2) [14].The prognostic impact of MMPSwas further evaluated in the intention to treat cohort without surgery (n=37)as well as in an independent cohort of patients treated at the Division of Thoracic Surgery, University Hospital in Vienna (n=22) with the same treatment approach of induction chemotherapy followed by EPP.

Results

From 1st May 1999 until August 2011, 186out of 323 MPM patients wereeligible and agreed to undergo induction chemotherapy followed by EPP**(Intention to treat (ITT) group):**The initial 63patients (34%) received three cycles of cis/gemandsince March, 2003,122patients (65%) were treated withcis/pem chemotherapy,onepatient received cisplatin plus vinorelbine. There was significantly less °III/°IVhaematological toxicity at day 8 after cis/pemchemotherapy ($p<0.0005$)in comparison to cis/gem, whilethere wereno significant differences in nephrotoxicity or unscheduled hospitalisations.Response after chemotherapy wasassessed in 128cases:60patients had stable disease (SD),33progressive disease (PD), and 35partial response (PR), no complete response was observed. There was no significant difference in response between the two chemotherapy regimens: 66% cis/gem with SD or PR versus77% cis/pem($p=0.7$). Also the changes of tumorvolume after chemotherapy did not

differ significantly (cis/gem 81% with tumor volume ≤500 ml vs. 86% cis/pem(Mann-Whitney U Test, p=0.8).

The median follow-up time of the ITT group(n=186) was 18months (1-123). Sixpatients were lost to follow up, leading to 97% complete follow-up. Median OSwas 19 months (95% CI: 15-23). Patients with progressive disease (n=33) had a significant shorter median OS(14 months (95% CI: 9-18)) in comparison to patients with PR/SD (n=95) (22 months (95% CI: 17-26)) (p=0.02) (Figure 1A).The chemotherapy regimen applied had no impact on OS (Figure 1B). 58 patients were excluded from radical resection after induction chemotherapy. The most frequent reason for exclusion was multi-level chest wall infiltration (n=26),another reason was progressive disease (n=18) (See supplementary figure 1).

128patients underwent **EPP after completion of 3 cycles of chemotherapy**corresponding to a resectability rate of 69%. The following analysisis based on thispopulation; patients' characteristicsare listed in table1. EPP was performed by three different surgeons in a median operation time of 360min (230–580 min). The mediastinal lymphadenectomy resulted in a mean number of 11 resected lymph nodes (regional and mediastinal) (SD ±9). The median duration of hospital stay was 15days (6–39). 6patients died within the first 30 days after operation (**30-day mortality** 4.7%) due to massive central pulmonary embolism (n=1), septic multiorgan failure (n=1), acute heart failure (n=2), pneumonia (n=1),and partial gastric necrosis due to herniation after patch failure (n=1). The latest case of 30 day mortality was2011after a period of 4years without any perioperative deaths.Major postoperative **morbidity**(pulmonary embolism, bleeding, bronchopleural fistula, empyema, patch failure) occurred in 47cases (37%). The median **OS** for all 128 patients was 22 months (95% CI: 20-24) and significantly differed from the survival of the patients treatedwith chemotherapy alone($p<0.0005$) (Figure 2) which might be attributed to the effect of surgery as well as to patient selection.Thesignificant results of univariate analyses ofOS are listed in table 2 and entered multivariate analysis (Table 3).

Side effects of radiotherapy included dysphagia (n=16), nausea (n=26), emesis (n=19), radiation dermatitis (n=9), fatigue (n=17), but also more important complication such as esophagitis (n=6).

In addition to the independent prognosticators of our multivariate analysis CRPand RECIST,we includedtumor volume and histological subtype into our proposed MMPSaccording to reports from the literature[12, 15].

The MMPSrevealed that patients with a score >3had a significantly shorterOS($p<0.0005$) (Figure 3A). The same was observed using the score without the response variable (data not shown).Multivariate analysis including our MMPSrevealed that the score was a strong independent prognosticator (table 3). The score was tested also in patients of the **ITT group**(n=37) that did not receive EPP after induction chemotherapyand validated in an independent cohort being treated with induction chemotherapy followed by EPP at the University Hospital Vienna (n=22), both cohorts not being significantly different in terms of age, pre chemotherapy volume, pre chemotherapy histological subtype, and RECIST.In these two cohorts patients with score 0 showed a significantly longer OS(Figure 3B and 3C), but median survival could not be calculated for all scores in the Vienna cohort, because 10 of 22 patients had to be censored in survival analysis.

The comparison of the present scores to EORTC score using ROC analysis at two years showed that the MMPS (3 and 4 variables) demonstrated a better predictive power for OS thanthe EORTC Score (Supplementary figure 2). Similar results were obtained for one year (data not shown).

Discussion

The present analysis isone of the largest series of induction chemotherapy followed by EPP and confirms a median survival of 22 months after induction chemotherapy with initiallycis/gem and in the later period cis/pem followed by EPP for MPM of all histological

subtypes and irrespective of nodal status. From these data we developed aMultimodality Prognostic Score considering four clinical variables available before surgery identifying mesothelioma-patients most likely not benefittingfrom multimodality treatment,which we were not able to demonstrate with existing scores as the EORTC score.

When we introduced induction chemotherapy followed by EPP as a treatment modality for MPM patients 12 years ago, we postulated that upfront chemotherapy may possibly downstage the tumor and hence increase resectability of MPM and therefore improve survival. In our initial pilot study we observed a promising median overall survival time of 22 months which was later confirmed by our Swiss multicentre study[2]. Since then this concept has been adapted by multiple other mesothelioma centersworldwide with comparable outcome[3, 4].However, overall survival for the whole cohort plateaued at nearly 2 years (reviewed in Cao et al. 2010 [16]). This is most likely related to the fact that eligibility criteria were wide. In additionpatients'selection became less stringent over time and patients with more advanced disease (proportion of pT4 10% in the present cohort) orcomorbidities were accepted. This was felt to be justified by the lack of alternatives and the fact that we were able to perform this complex treatment with relatively low mortality and morbidity. Patients were accepted for induction chemotherapy and later for resection evenifno response to chemotherapy occurred. However, our current analysis shows, that such "rescue procedures" resulted in no long-term benefit and we might have observed better outcome with less wide inclusion criteria.

The currentanalysis represents12years' experience with cisplatin-based induction chemotherapy followed by EPP in patients with mesothelioma.To our knowledge, although not randomized, this is the first series reporting a large cohort of patients who received platinum-based chemotherapy in combination with either gemcitabine or pemetrexed asinduction chemotherapyfollowed by EPP. In our analysis we focused not primarily on identification of prognostic factors based on pathological staging but rather on prognostic

factors available at initial patient evaluation.Nowadays well-defined selection criteria for mesothelioma treatment would be of key importance, as clinical staging is unreliable in MPM and therefore of limited help for patient selection.

One particular patient subgroup of interest isthe one responding to induction chemotherapy. Indeed, the response to chemotherapy significantly influenced OS– 2/3 of the patients responded with either PR or SD afterinduction chemotherapy and survived significantly longer. Response to chemotherapy turned out to beeven an independent prognosticator in our multivariate analysis,which could help to select patients for surgery.The use of cis/gem compared to cis/pem had no influence either on response to chemotherapy measured by RECIST oron survival. But it was found that toxicity differsbetween the two regimens and °III/°IV haematological toxicity was significantly lower after cis/pem.

Since Pass et al. proposed to use tumor volume as a prognostic factor for mesothelioma patients' survival [13], it has been confirmed by several other groups [12]. Modern computer-based software using chest CT facilitates tumormeasurement in a reliable and reproducible way[9]. In addition, low C-reactive protein level (CRP)was identified as independent prognosticator for longer OS. CRP as an easy to measure marker of inflammatory response has been validated already in various other cancers as a prognostic marker[17, 18]. The reason why CRP is a prognostic value in cancer patients is not completely understood but might be related to higher tumor aggressiveness as it has been shown also for other type of tumors, eg. melanomaand was already demonstrated to be prognostic in the context of MPM [19].

Other prognosticators such as histological subtype ormediastinal lymph node involvement which are quite uniformly reported to have an impact on MPM patients' survival (reviewed in Cao et al. 2011 [20]), were not confirmed as independent prognosticators in our multivariate analysis.This was also observed in the retrospective analysis of the IASLC database – the biggest dataset with more than 3101 patients from 15 centres. But for obvious reasons, theprognostic meaning of a mesothelioma lymph node metastasis in the mediastinum is not

comparable to lung cancer given the direct neighbourhood of the primary tumor in the pleura to the mediastinum.

Because histology could not be confirmed as an independent prognostic factor in our analysis as well as in different phase II studies[2-4, 21-23], we proposethat inclusion of a patient into multimodality treatment should not be based on a single factor alone– such as histological subtype or lymph node metastasis–but should rather respect a combination of various factors.Based on our analysis, our clinical experience with this heterogeneous disease, andwith respect to the published literature[12, 13, 19],we proposethis"Multimodality Prognostic Score" using parameters being available before surgery or at initial patient evaluation. The MMPS (using 3 or 4 variables) clearly stratifiedpatients: Patients with score 0 had in all 3 cohorts tested the longest OS, whereas patients with a score of 3 or higher had OS as dismal as untreated MPM patients.Furthermore, this was not only confirmed in our ITT group of patients not undergoing EPP, but also in a second independent cohort of patients treated with the same protocol in Vienna.

In the last years a clear trend to replace EPP by (extended) pleurectomy/decortication (P/D), especially for early stages, exists.We hypothesize, that this score may be applicable to all macroscopic complete resections (MCRs) within a multimodality concept, as a small subset of patients excluded from EPP received P/D (n=20) instead and here we could observe a trend ofsurvival prognostication by our MMPS score (data not shown).

Although EORTC Score has been validated in several cohorts[24], we were not able to demonstrate any significant prognostic impact on OS.This may be explained by our median EORTC score which was 0.6 (range 0-2.34) and quite low in comparison to other groups. The higher scores in the other groups are probably due to the fact that these cohorts were receiving chemotherapy alone in most cases and therefore had advanced disease and worse performance status.In comparative ROC analysis our MMPS score performed better than EORTC score.

Besides the retrospective analysis of our data and the fact that therefore not all data were available for the whole patient cohort, we are aware that AUC of 69% does not qualify our MMPS immediately as a predictive test for patient selection. However, confirmation in an independent cohort and in a patient cohort intended to be treated warrants further prospective evaluation. With a specificity of 100% of Score 3 and 4 (no survivor had this score) and a survival resembling untreated MPM patients, we feel that these patients should not be recommended to proceed to MCR in a multimodality concept, which will now be further evaluated prospectively.

Conclusion: Overviewing our 12 years' experience with induction chemotherapy with cis/gem and cis/pemfollowed by EPP for MPM patients of all histological subtypes including N2 disease,we report a median OS close to two years. The non-randomized comparison of both chemotherapy regimens showed significant reduced haematological toxicity in favour of cis/pem but no advantage in response or overall survival. A new Multimodality Prognostic Score was developed and validated in an independent cohort considering clinical variables already available before surgerywhich allowsidentification ofmesothelioma-patients who would not get any relevant benefit from an intensified therapy. Additionally biological markers are intensively explored at our institution. Among these, tumor proliferation index is a robust biomarker, and was significantly associated with clinical outcomes and tumor volume. We are also validating the previously identifiedprognostic microRNA score [25] in our patient cohort. This is particularly interesting as microRNAs are also potential blood based biomarkers[26]. Thus, we may improve the prognostic value by integrating these factors into our Multimodality Prognostic Score. The conceptwill be further validated prospectively.

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Figure legends

Figure 1:

Kaplan-Meier curve of overall survival time in months including all patients intended to be treated with chemotherapy followed by EPP. (A) Comparison of response to chemotherapy using modified RECIST criteria: Median survival time 22 months (95% CI: 17-26) with stable disease (SD) or partial response (PR) versus median survival time 14 months (95% CI: 9-18) with progressive disease (PD). Response data was only available for 128 patients of the ITT group.(B) Comparison of chemotherapy regimen applied: Median survival time 21 months (95% CI: 15-26) with cisplatin / gemcitabine (cis/gem) versus median survival time 18 months (95% CI: 12-24) with cisplatin / pemetrexed (cis/pem).

Figure 2:

Kaplan-Meier curve of overall survival time in months of patients treated with induction chemotherapy alone vs induction chemotherapy followed by EPP.Median survival time 22 months (95% CI: 20-24) with EPPversus median survival time 10 months (95% CI: 9-12) without EPP.

Figure 3:

Kaplan-Meier curve of overall survival (OS) in months of the multimodality prognostic score (including 4 variables: tumor volumepre CTX > 500ml, CRP pre CTX > 30mg/l, non-epithelioid histology in pre CTX biopsy, progressive disease according to modified RECIST criteria): (A) patients treated with induction chemotherapy followed by EPP (Zurich). (B) Patients of the intention to treat group (Zurich). (C) Patients treated with induction chemotherapy followed by EPP (Vienna).

Supplementary figure 1

Flowchart of patients referred to University Hospital Zurich with diagnosis of MPM between May 1999 and August 2011.

* 59 patients of 128 had all 4 items of the MMP score available

** Out of 58 patients excluded to undergo EPP, 26 patients were excluded before and 32 during surgery.

Supplementary figure 2

ROC analysis at two years: the Multimodality Prognostic Score (4 variables) demonstrated the best predictive power for OS (AUC 0.687 95% CI 0.54–0.835) followed by the Multimodality Prognostic Score (3 variables) (AUC 0.677 95% CI 0.538–0.816) and the EORTC Score (AUC 0.519 95% CI 0.392–0.646). The differences were not significant.

MMPS-4: Multimodality Prognostic Score (4 variables)

MMPS-3: Multimodality Prognostic Score (3 variables)

EORTC: EORTC score

AUC: Area under the curve

Tables

Value		Number (percent)
Gender (male)		113 (88%)
Age (</= 61 years)		67 (52%)
Side of Disease (right)		72 (56%)
Asbestos exposure		101 (79%)
Smoking		66 (52%)
Weight loss		49 (38%)
Chest pain		56 (44%)
ECOG PS*	0	62 (60%)
	1	31 (30%)
	2	10 (10%)
White blood cell count*(> 9.6 G/l)		36 (33%)
Hemoglobin concentration*(≤ 117 g/l)		23 (21%)
Platelet count*(> 400 G/l)		43 (40%)
CRP level*(> 30 mg/l)		46 (44%)
EORTC score*(> 1.15)		40 (48%)
Histologigal subtypepre chemotherapy	Epithelioid	102 (80%)
	Sarcomatoid	4 (3%)
	Biphasic	21 (17%)
Mediastinoscopy		107 (84%)
cN2 at mediastinoscopy		8 (7%)
Chemotherapy	cis / gem	47 (37%)
	cis / pem	81 (63%)
severe side effects		34 (27%)
hemotoxicity		19 (15%)
nephrotoxicity		8 (6%)
hospitalisation		11 (9%)
RECIST*	Partial regression	33 (36%)
	Stable disease	34 (37%)
	Progressive disease	25 (27%)
Tumor volumepre chemotherapy* (> 500 ml)		7 (10%)
Tumor volumepost chemotherapy* (> 500 ml)		7 (9%)
Surgery	major morbidity	47 (37%)
	30 day mortality	6 (5%)
Resection*	R0/R1	116 (95%)
	R2	6 (5%)
Histotypepost chemotherapy	Epithelioid	80 (63%)
	Sarcomatoid	4 (3%)
	Biphasic	44 (34%)
ypT stage	1	11 (9%)
	2	40 (31%)
	3	64 (50%)
	4	13 (10%)
ypN stage	0	82 (64%)
	1	16 (13%)
	2	29 (23%)
IMIG	1	11 (9%)
	2	29 (23%)
	3	75 (58%)
	4	13 (10%)
Trocar infiltration*		24 (22%)
Adjuvant radiotherapy		67 (52%)
Side effects		32 (48%)

Table 1: Patients' characteristics of the group receiving induction chemotherapy and EPP (n=128).
* Data were not available for all 128 patients

	Factor	Median survival in months (95% CI)	P
OS	Age	≤61 years: 20 (16-25) >61 years: 23 (19-28)	0.03
	CRP level*	≤ 30 mg/l: 23 (20-26) > 30 mg/l: 17 (9-25)	0.03
	RECIST*	PR/SD: 22 (21-24) PD: 14 (10-19)	0.008
	Multimodality Prognostic Score*	Score ≤ 2: 21 (15-28) Score > 2: 4 (3-5)	< 0.0005
	ypT-stage	ypT1: 39 (13-66) ypT2: 23 (20-25) ypT3: 22 (17-26) ypT4: 15 (9-20)	0.02
	nodal status (ypN0 vs. ypN1/2)	ypN0: 23 (20-27) ypN1/2: 19 (14-24)	0.007
	lymph node ratio	0.00: 23 (20-27) ≥ 0.01: 19 (14-24)	0.008
	trocar infiltration*	No: 23 (21-24) Yes: 15 (6-23)	0.02
	IMIG-stages	I: 39 (13-66) II: 26 (19-32) III: 22 (19-24) IV: 15 (9-20)	0.01

Table 2: Kaplan Meier overall survival analysis of prognostic factors for 128 patients undergoing induction chemotherapy and EPP.
Data are given as median survival in months (starting from first cycle of chemotherapy received) with 95% confidence interval
* Data were not available for all 128 patients
Multimodality Prognostic Score including 4 variables: tumor volume pre CTX > 500ml, CRP pre CTX > 30mg/l, non-epithelioid histology in pre CTX biopsy, progressive disease according to modified RECIST criteria
CRP: C-reactive protein, PR: partial response, SD: stable disease, PD: progressive disease

		HR (95% CI)	p
OS	MultimodalityPrognostic Score (4 variables, Score ≤ 2 vs. Score > 2)	14.1 (4.0-85.1)	<0.0005

Table 3: Multivariate Cox regression analysis of prognostic factors with significant influence on OS in the univariate analysis, excluding factors being represented in the score.
Data are given as hazard ratio with 95% confidence interval
Multimodality Prognostic Score including 4 variables: tumor volume pre CTX > 500ml, CRP pre CTX > 30mg/l, non-epithelioid histology in pre CTX biopsy, progressive disease according to modified RECIST criteria

Figure 1.

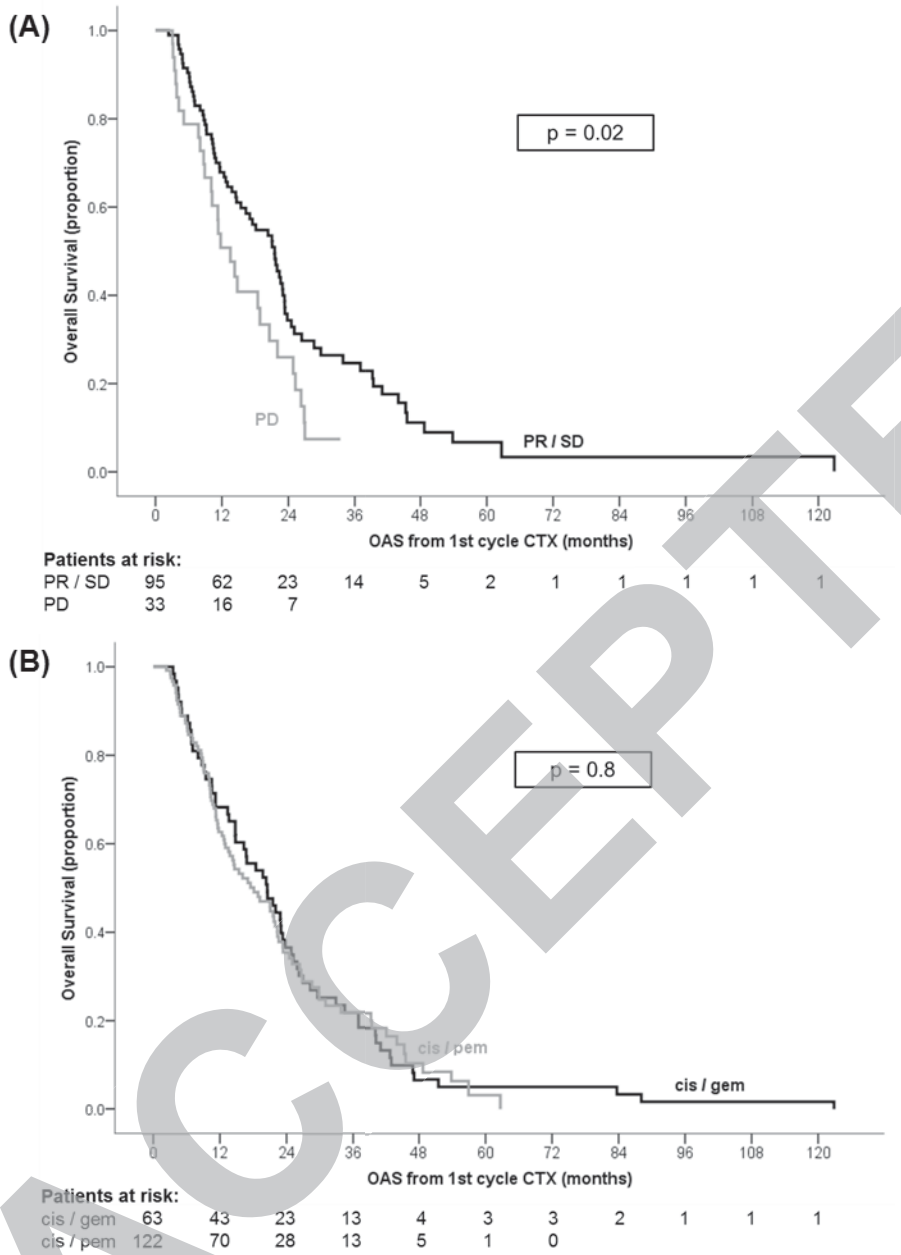
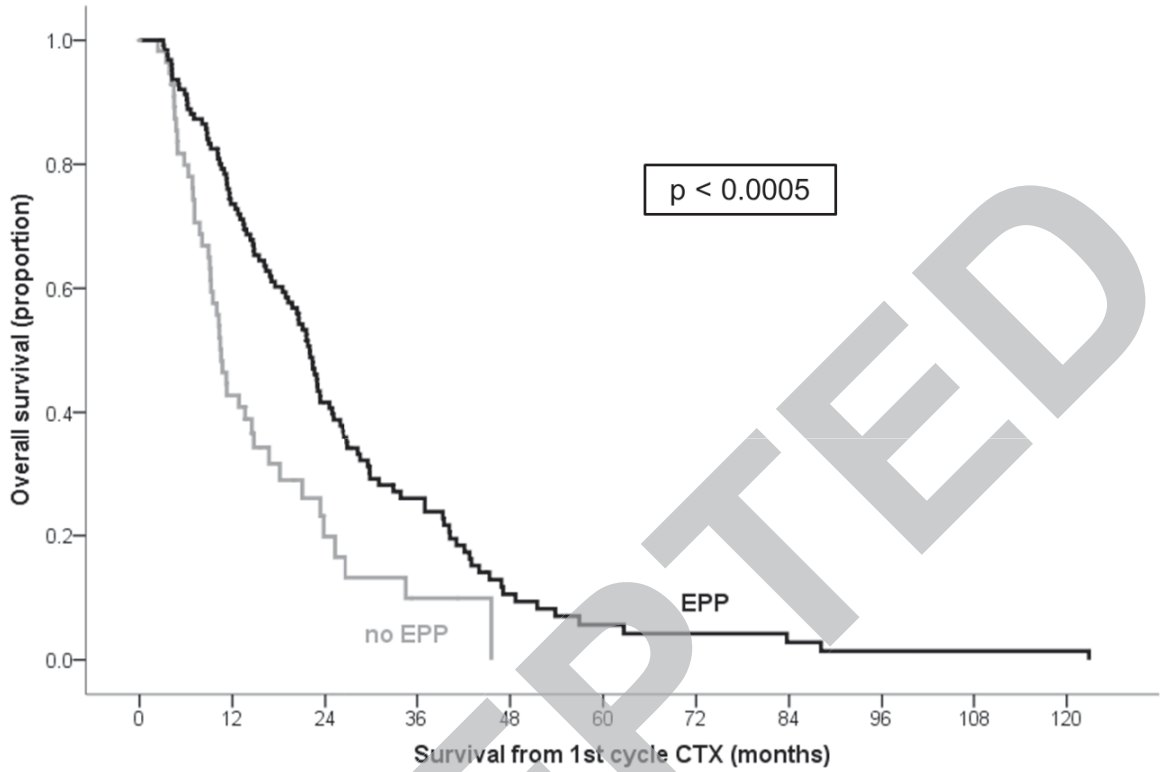


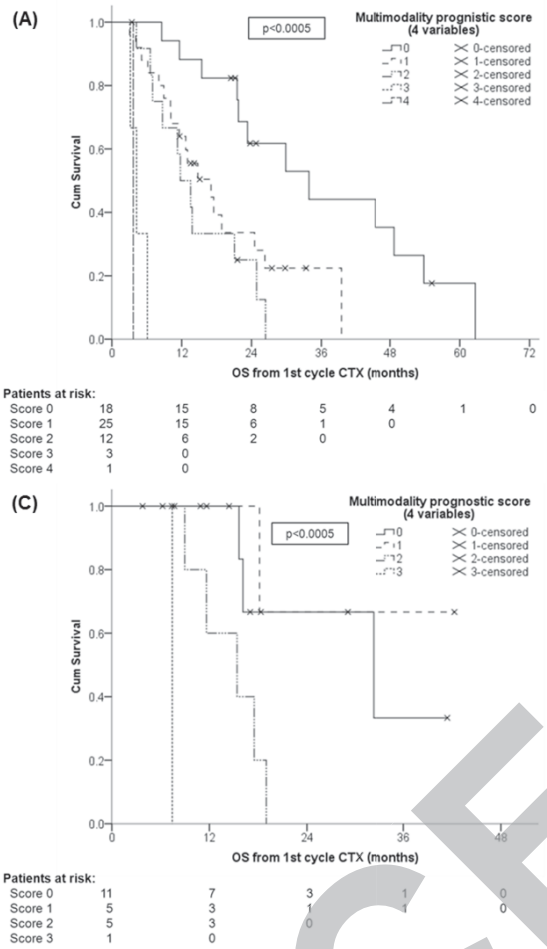
Figure 2.



Patients at risk:

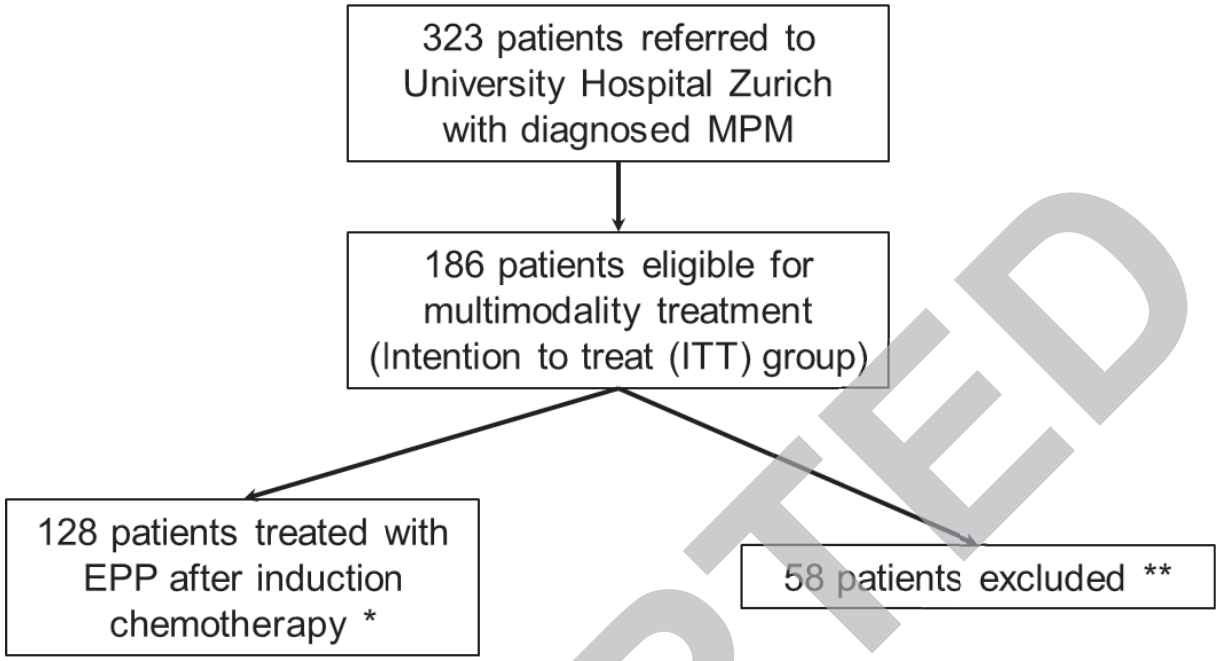
EPP	128	90	45	24	9	4	3	2	1	1	1
No EPP	58	23	6	2	0						

Figure 3.



	(A) Patients treated with induction chemotherapy followed by EPP (Zurich)	(B) Patients of the intention to treat group (Zurich)	(C) Patients treated with induction chemotherapy followed by EPP (Vienna)
number of patients	59	37	22
	Median survival time in months (95% CI)		
Score 0	34 (18-50)	21 (6-36)	32 (8-56)
Score 1	17 (9-25)	11 (7-14)	- (-)
Score 2	12 (8-16)	10 (8-12)	15 (7-24)
Score 3	4 (3-6)	10 (0-21)	7 (-)
Score 4	4 (-)	3 (-)	

Suppl_Fig 1.



Suppl_Fig 2.